Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study

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Summary

Background The contributions of as-needed inhaled corticosteroids and long-acting β2 agonists (LABA) to asthma control have not been fully established. We compared the efficacy and safety of three reliever strategies: a traditional short-acting β2 agonist; a rapid-onset LABA (formoterol); and a combination of LABA and an inhaled corticosteroid (budesonide-formoterol) in symptomatic patients receiving budesonide-formoterol maintenance therapy.

Methods We did a 12-month, double-blind, parallel-group study in 3394 patients (aged 12 years or older), in 289 centres in 20 countries, who were using inhaled corticosteroids at study entry and symptomatic on budesonide-formoterol (160 μg and 4·5 μg, respectively), one inhalation twice daily, during a 2-week run-in. After run-in, patients were randomly assigned budesonide-formoterol maintenance therapy plus one of three alternative as-needed medications—terbutaline (0·4 mg), formoterol (4·5 μg), or budesonide-formoterol (160 μg and 4·5 μg). The primary outcome was time to first severe exacerbation, defined as an event resulting in hospitalisation, emergency room treatment, or both, or the need for oral steroids for 3 days or more.

Findings Time to first severe exacerbation was longer with as-needed budesonide-formoterol versus formoterol (p=0·0048; log-rank test) and with as-needed formoterol versus terbutaline (p=0·0051). The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide-formoterol, respectively (rate ratios budesonide-formoterol versus formoterol 0·67 [95% CI 0·56–0·80; p<0·0001]; budesonide-formoterol versus terbutaline 0·52 [0·44–0·62; p<0·0001]; formoterol versus terbutaline 0·78 [0·67–0·91; p=0·0012]). Asthma control days increased to a similar extent in all treatment groups. As-needed formoterol did not significantly improve symptoms compared with as-needed terbutaline. All treatments were well tolerated.

Interpretation Both monocomponents of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance.

Introduction

Over the past decade, maintenance treatment in patients with persistent asthma has evolved from inhaled corticosteroids alone to combination therapy with long-acting β2 agonists (LABA). This move has led to improved symptom control and a reduced need for higher doses of inhaled corticosteroids.[1–3] However, despite evidence that add-on LABA therapy can reduce exacerbations by 3–14% compared with higher doses of inhaled corticosteroids,[1,4] the dose of inhaled steroid at which the addition of LABA is most beneficial has not been clearly established.[1]

This dilemma could be overcome if a pragmatic way of delivering increased anti-inflammatory therapy at the first sign of increased symptoms were found, rather than relying on as-needed short-acting β2 agonists. In clinical studies, the use of a combination of inhaled corticosteroids and LABA (budesonide-formoterol) in one inhaler for both maintenance and as-needed therapy reduced the risk of experiencing severe exacerbations by 39–54% compared with a higher maintenance dose of budesonide,[5–8] by 45% compared with fixed-dose budesonide-formoterol,[9] and by 25% compared with a higher dose of salmeterol-fluticasone.[10] Moreover, this novel treatment approach reduced both inhaled corticosteroids and oral corticosteroid exposure, with a similar or reduced effect on morning plasma cortisol and adrenal function, compared with budesonide 800 μg per day.[9,10]

This simplified approach is possible because formoterol provides rapid symptom relief,[11–14] with the result that a separate short-acting β2 agonist is not needed. However, the mechanism underlying the reduction in exacerbations seen with budesonide-formoterol maintenance and reliever therapy is not fully understood. As-needed formoterol was shown to reduce asthma exacerbations compared with terbutaline in a large, double-blind study in asthma patients with a persistent high use of reliever therapy despite using regular inhaled corticosteroids.[14] However, whether patients on combination therapy would experience such a benefit was not clear. Additionally, the specific contribution of the as-needed budesonide component of budesonide-formoterol for maintenance and relief has not been assessed. The present 12-month, double-blind study was therefore done in patients with moderate to severe persistent asthma who remained symptomatic on regular budesonide-formoterol

combination maintenance therapy, to assess the add-on efficacy of three alternative reliever medications—budesonide-formoterol, formoterol, and terbutaline.

Methods

Patients

Outpatients aged 12 years or older with a clinical diagnosis of asthma[15] for at least 6 months were enrolled if they had had more than one severe asthma exacerbation in the 12 months before entry. All patients had used inhaled corticosteroids for at least 3 months and at a constant dose for 4 weeks or more immediately before entry. Inclusion criteria also included a forced expiratory volume in 1 s (FEV_1) 50–100% of predicted normal (prebronchodilator) with 12% reversibility or more (and an increase in basal FEV_1 of 200 mL or more if aged 18 years or older) after inhalation of terbutaline 1 mg. Exclusion criteria included any respiratory infection affecting the patient's asthma or use of oral corticosteroids within 1 month of study entry. To be eligible for randomisation, patients had to have used reliever medication on 5 or more of the last 7 days of run-in, but no more than ten inhalations on any one day.

Study design

Our 12-month, double-blind, randomised parallel-group study was done in 289 centres in 20 countries: Belgium (21 centres), Bulgaria (11), China (6), Czech Republic (34), Germany (26), Greece (9), Hungary (20), Indonesia (6), Italy (6), Malaysia (3), The Netherlands (30), Norway (17), the Philippines (11), Poland (18), Romania (12), Russia (11), Slovakia (12), South Africa (30), South Korea (4), and Vietnam (2). The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol, patient information, and consent forms. All patients and parents or guardians of underage children gave written informed consent.

Patients attended clinic visits at the beginning and end of run-in, and after 1, 4, 8, and 12 months of treatment (visits 1–6). During a 2-week run-in period, patients used budesonide-formoterol 160/4·5 μg (symbicort turbuhaler, AstraZeneca, Lund, Sweden), one inhalation twice a day, plus terbutaline 0·5 mg (metered dose; delivered dose 0·4 mg; bricanyl turbuhaler, AstraZeneca) for reliever medication. After run-in, all patients continued to use budesonide-formoterol 160/4·5 μg, one inhalation twice a day for maintenance therapy and were randomly assigned to treatment with one of three reliever medications (1:1:1 ratio) for 12 months: additional inhalations of budesonide-formoterol 160/4·5 μg; formoterol 4·5 μg (oxis turbuhaler, AstraZeneca); or terbutaline 0·4 mg. All as-needed study medication was given via identical turbuhaler inhalers, all matched in appearance to the symbicort turbuhaler.

The randomisation schedule was computer generated at AstraZeneca Research and Development, Charnwood, UK, by a person independent of the study team. Within each centre, eligible patients were sequentially assigned a randomisation code by the investigator from the computer-generated list.

Patients were instructed to use their reliever medication for asthma symptoms but not for prophylaxis. During the treatment, patients were not to use more than ten inhalations of reliever medication a day. If more than ten inhalations were needed in one day, patients were told to contact the investigator for reassessment.

Procedures

The primary outcome measure was time to first severe exacerbation. The total number of severe exacerbations, number of days with hospitalisation, emergency room treatment, or both, and days with oral steroids because of exacerbations were recorded. Secondary outcomes included total number of severe exacerbations, time to first and total number of emergency treatment or hospitalisations, asthma symptom scores—asthma control questionnaire (five-item symptom and activity version; ACQ-5) score;[16] mild exacerbations; FEV_1; morning and evening peak expiratory flow (PEF); and reliever medication use. Patients completed a daily diary throughout the study in which they recorded asthma symptoms during the night and daytime (on a three point scale, with 0 indicating no symptoms and three indicating incapacitating symptoms). These scores were added to obtain the total daily asthma symptom score (range 0–6). Nights with awakenings due to asthma, the number of inhalations of reliever medication, and intake of maintenance medication were also recorded on diary cards. The percentage of asthma-control days (a night and a day with no asthma symptoms, no intake of reliever medication, and a night with no awakenings due to asthma symptoms) were assessed. The ACQ-5 was completed by patients at every clinic visit, with all five questions scored on a scale of 0 to 6 (where 0 represents good control and 6 represents poor control).[16]

At each clinic visit, the best of three satisfactory FEV_1 tests was recorded. Patients recorded the best of three PEF measurements with a Mini-Wright peak flow meter (Clement Clarke, Harlow, UK) on rising in the morning and before going to bed. Adverse events reported spontaneously and in response to a standard question at visits 2–6 were recorded.

A severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for 3 days or more (as judged by the investigator). A mild exacerbation day was defined as fulfilment of at least one of the following criteria, based on 24 h diary data: any night with awakenings due to asthma; morning PEF 20% or more below baseline (average of previous 10 days before the day of randomisation) of morning PEF; as-needed medication use of two inhalations or more in 24 h above baseline (the average of previous 10 days before the day of randomisation).

A mild exacerbation was defined as two consecutive mild asthma exacerbation days satisfying the same criterion.

Statistical analysis

The primary objective was to compare budesonide-formoterol maintenance and as needed versus budesonide-formoterol with formoterol as needed. A secondary objective was to compare budesonide-formoterol for maintenance and as needed with budesonide-formoterol with terbutaline as needed. The primary outcome variable was time from randomisation to the first severe asthma exacerbation. With a total of 1000 patients per group, a log-rank test (at the two-sided 5% significance level) had a 90% chance of detecting a difference, assuming a true difference of 25% versus 19% in the proportion of patients with severe exacerbation. All patients for whom data were recorded after randomisation were included in the full analysis set, which was used for all efficacy analyses. The safety analyses were based on all patients who received one dose or more of the randomised study drug and who had data recorded after randomisation.

The time to first severe exacerbation was described with Kaplan–Meier curves and was compared between treatments with a log-rank test. Further description of treatment differences was obtained with a Cox proportional hazards model stratified by country and with treatment as factor.

Several secondary outcome variables were used to further compare the efficacy of the three treatments. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model, with treatment and country as factors and time in the study as an offset variable. Time to first mild exacerbation and the total number of mild exacerbation days were analysed in the same way as severe exacerbations.

Changes in diary-card variables from the average value during run-in (average value over the previous 10 days of run-in) to the average value during treatment were

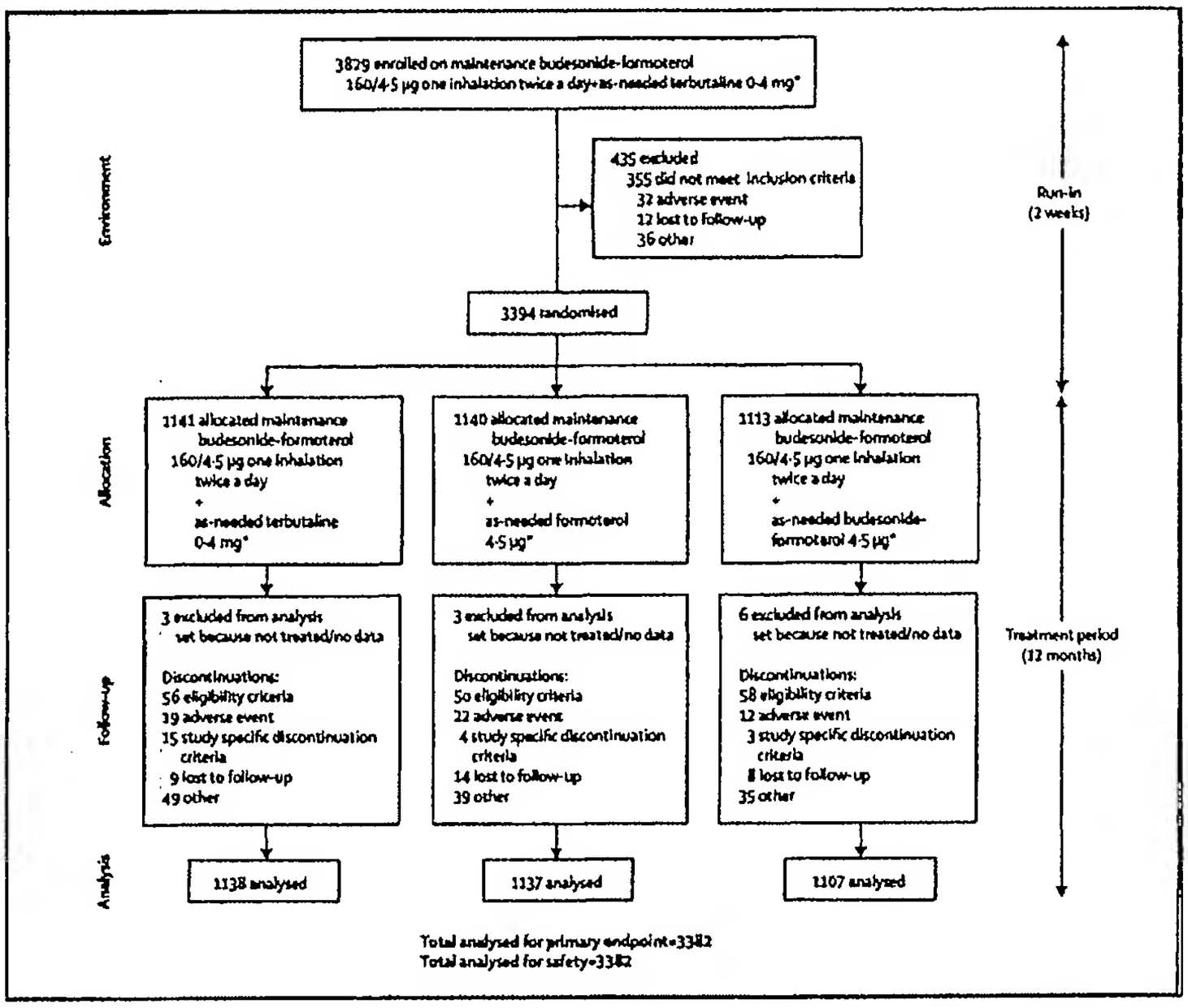

Figure 1: Trial profile
*0·4 mg delivered dose corresponds to 0·5 mg metered dose.

	Terbutaline as-needed group (n=1141)	Formoterol as-needed group (n=1140)	Budesonide-formoterol as-needed group (n=1113)
Men, n (%)	450 (39%)	458 (40%)	437 (39%)
Age, years	43 (12–83)	42 (12–81)	42 (12–89)
Median (range) asthma duration, years	10 (1–69)	10 (1–77)	9 (0–64)
FEV, L	2·16 (0·68–4·58)	2·20 (0·74–4·58)	2·21(0·61–4·68)
FEV, (pre-terbutaline), % predicted	72 (39†–100)	72 (38†–115†)	72 (30†–110†)
FEV, reversibility, %	24 (11†–90)	24 (0†–96)	24 (6†–132)
ICS dose at entry, µg/day	751 (250†–1600)	758 (320†–1600)	757 (160†–1600)
Inhaled LABA use at entry, % of patients	59%	59%	59%
Mean daily asthma control measures ‡			
Total asthma symptom score (scale 0–6)	1·74 (0·00–6·00)	1·70 (0·00–6·00)	1·71 (0·00–6·00)
Reliever use, number of inhalations per 24 h	3·9 (0·3–9·7)	3·9 (0·0–9·1)	3·8 (0·0–8·9)
Nights with awakenings, %	30·3 (0–100)	28·0 (0–100)	31·1 (0–100)
Asthma-control days§, %	8·3 (0–50)	8·3 (0–80)	9·2 (0–90)
ACQ-5¶	1·9 (0·4–8)	1·9 (0·5–8)	1·9 (0·4–8)

Data are mean (range) unless otherwise indicated. ACQ-5=Asthma control questionnaire (5-item symptom and activity version). FEV,=forced expiratory volume in 1 s. ICS=inhaled corticosteroid. LABA=long-acting β2 agonist. *All patients received budesonide-formoterol 160/4·5 µg one inhalation twice daily for maintenance therapy. †Deviation from inclusion criteria (included in all statistical analyses). ‡Average over the past 10 days of run-in. §A night and day with no asthma symptoms (symptom score=0), a night with no awakenings due to asthma symptoms, and a night and day with no use of as-needed medication. ¶ACQ-5 was measured at visit 2.

Table 1: Baseline characteristics of patients using maintenance budesonide-formoterol plus alternative reliever medications*

compared between treatments with an ANOVA model with treatment and country as fixed factors and the run-in period average as a covariate. Changes in FEV, and ACQ-5 were analysed with a similar ANOVA, with the end of run-in value as a covariate. Results for secondary outcome variables are reported with nominal p values, without any adjustment for multiple tests. Adverse events were analysed with descriptive statistics and qualitative analysis.

Role of the funding source

The sponsors of the study were involved with the study design, interpretation of the data, and the decision to submit the paper for publication in conjunction with the study investigators. Employees of the sponsor collected and managed the data, and performed the data analysis. The corresponding author had access to the full clinical trial database and all authors had free access to the clinical study report and the results of the statistical analyses. Employees of the sponsor reviewed drafts of the manuscript and made editing suggestions. All authors made final decisions on all aspects of the manuscript.

Results

The first patient was enrolled into the study on April 10, 2003, and the last patient completed the study on Dec 21, 2004. Of the 3829 patients enrolled in the study, 3394 were randomised. Of the 435 patients (11%) who were not randomised, 355 did not satisfy eligibility criteria, 32 had an adverse event, 12 were lost to follow-up, and 36 discontinued for other reasons. The full analysis set included all randomised patients who provided any data after randomisation. Data were not obtained for 12 randomised patients before they left the study. Therefore, 3382 patients were included in the efficacy and safety analyses (figure 1). There were 474 patients with one protocol deviation or more, with a similar distribution across groups. The mean number of protocol deviations per patient was 0·2 (range 1–10); none of the deviations justified exclusion of data from the analysis. Baseline characteristics were comparable

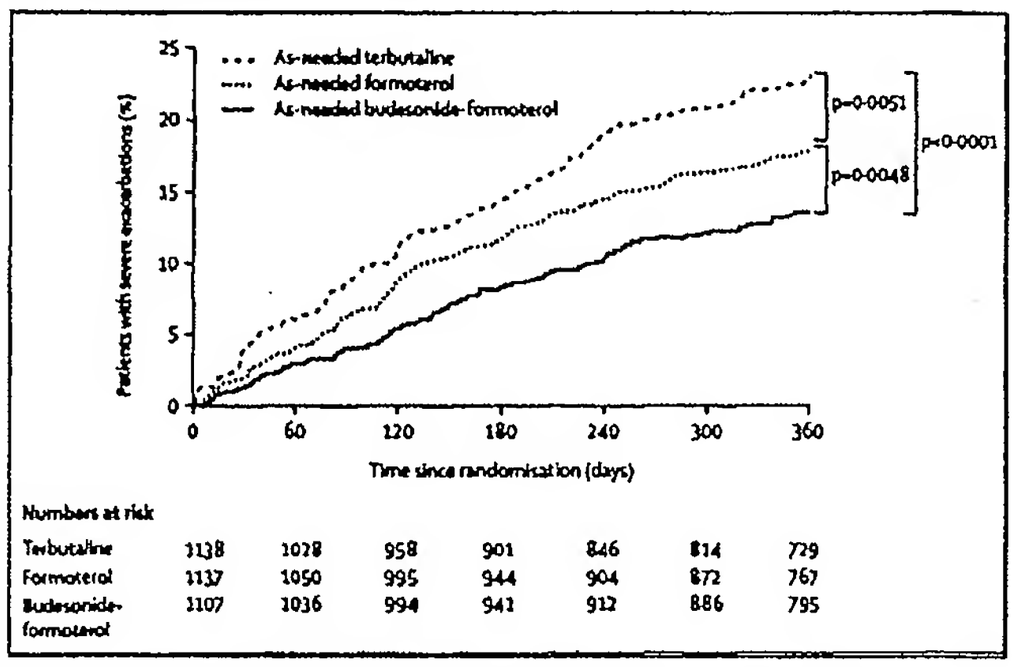

Figure 2: Kaplan–Meier plot of time to first severe asthma exacerbation
Time to first severe asthma exacerbation defined as a deterioration in asthma resulting in hospitalisation, emergency room treatment, or the need for oral steroids for 3 days or more because of asthma (as judged by investigator). Patients received maintenance budesonide-formoterol 160/4·5 µg, one inhalation twice daily, plus one of the following for as-needed relief: additional inhalations of budesonide-formoterol 160/4·5 µg; formoterol 4·5 µg; or terbutaline 0·4 mg. Significant between-group differences were derived from a log-rank test.

	Reliever medication group			Treatment comparison of hazard ratios (95% CI)		
	Terbutaline as-needed (n=1138)	Formoterol as-needed (n=1137)	Budesonide-formoterol as-needed (n=1107)	Formoterol versus terbutaline	Budesonide-formoterol versus terbutaline	Budesonide-formoterol versus formoterol
Severe exacerbations (all definitions)						
Patients with event, n (%)	245 (22%)	195 (17%)	143 (13%)	0·76* (0·63–0·92); p=0·004	0·55* (0·45–0·68); p<0·0001	0·73* (0·59–0·90); p=0·0038
Total events (days with events)	377 (3030)	296 (2214)	194 (1353)			
Rate, events per 100 patients per year	37	29	19	0·78† (0·67–0·91); p=0·0012	0·52† (0·44–0·62); p<0·0001	0·67† (0·56–0·80); p<0·0001
Emergency room visits or hospitalisations						
Patients with event, n (%)	93 (8%)	75 (7%)	54 (5%)	0·79* (0·58–1·07); p=0·12	0·57* (0·41–0·81); p=0·0013	0·73* (0·51–1·04); p=0·079
Total events (days with events)	115 (392)	98 (282)	70 (218)			
Rate, events per 100 patients per year	7	5	4	0·83† (0·63–1·08); p=0·17	0·61† (0·45–0·82); p=0·0010	0·73† (0·54–0·99); p=0·046
Mild exacerbations						
Patients with event, n (%)	887 (78%)	873 (77%)	811 (74%)	0·97* (0·88–1·06); p=0·47	0·88* (0·80–0·97); p=0·0075	0·91* (0·83–1·00); p=0·050
Rate, days per patient per year	69	63	57	0·91† (0·83–1·00); p=0·058	0·82† (0·74–0·91); p=0·0001	0·90† (0·81–1·00); p=0·043

All patients received budesonide-formoterol 160/4·5 µg one inhalation twice daily for maintenance therapy. *Treatment comparisons of hazard ratios from a Cox proportional hazards model of time to first severe exacerbation. †Comparisons of relative rates from a Poisson regression.

Table 2: Severe and mild asthma exacerbations in patients using maintenance budesonide-formoterol plus alternative reliever medications

See Online for webtable

between groups (table 1). Self-reported adherence to maintenance medication was equally high in all groups (99% of patients had an average use of at least 1·71 maintenance inhalations per day).

The time to first severe exacerbation was prolonged with budesonide-formoterol for maintenance and relief versus budesonide-formoterol plus formoterol (p=0·0048, log-rank test) or terbutaline (p<0·0001; figure 2). As-needed formoterol prolonged the time to first severe exacerbation versus terbutaline (p=0·0051). As-needed budesonide-formoterol reduced the instantaneous risk of a severe exacerbation by 27% (95% CI 10–41%) versus formoterol and by 45% (32–55%) versus terbutaline. The risk reduction with as-needed formoterol versus terbutaline was 24% (8–37%). There were 867 severe exacerbations during the study (table 2). The yearly rate per patient was reduced with as-needed budesonide-formoterol by 33% versus formoterol (20–44%; p<0·0001), by 48% versus terbutaline (38–56%; p<0·0001), and by 22% with as-needed formoterol versus terbutaline (9–33%; p=0·0012; table 2). Rates of exacerbations needing emergency room treatment or hospitalisation—the most robust definition of exacerbations—were also reduced with as-needed budesonide-formoterol by 27% (1–46%; p=0·046) versus formoterol and by 39% (18–55%; p=0·0010) versus terbutaline, respectively. There was no significant difference between formoterol and terbutaline in this outcome (table 2). The proportion of patients with more than one exacerbation was low in all three treatment groups and lowest in the as-needed budesonide-formoterol group (3%, 7%, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively; webtable). Mild exacerbation days, a composite measure of poor control days, were reduced by 10–18% with as-needed budesonide-formoterol compared with both formoterol (p=0·043) and terbutaline (p<0·0001). The time to first mild exacerbation (defined as two consecutive mild exacerbation days satisfying the same criterion) was also longer with as-needed budesonide-formoterol versus terbutaline (p=0·0080) but the difference between as-needed budesonide-formoterol and formoterol was not significant (p=0·059). Mean asthma symptom scores decreased from run-in for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group versus maintenance therapy plus formoterol (p=0·0002) or terbutaline (p=0·0007; table 3). Night-time awakenings were reduced by 2% (7 nights per year) with as-needed budesonide-formoterol versus formoterol (p=0·018) and by 3% versus terbutaline (p=0·0025). Improvements were maintained during the 12-month study (webfigure). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores or night-time awakenings (table 3). Asthma-control days (days without symptoms or reliever use) increased in all groups from run-in, with no between-group differences (table 2). Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (p=0·0009) and terbutaline (p<0·0001). No difference in overall ACQ-5 scores was seen with formoterol versus terbutaline (table 3).

See Online for webfigure

Mean FEV_1 improved in each of the treatment groups during run-in when all patients used maintenance budesonide-formoterol plus as-needed terbutaline. After

	Change from run-in			Treatment comparison (95% CI); p*		
	Terbutaline as-needed (n=1138)	Formoterol as-needed (n=1137)	Budesonide-formoterol as-needed (n=1107)	Formoterol versus terbutaline	Budesonide-formoterol versus terbutaline	Budesonide-formoterol versus formoterol
Symptom control						
Asthma symptom score (scale 0–6)†	−0·58	−0·57	−0·69	0·01 (−0·05 to 0·07); p=0·72	−0·11 (−0·17 to −0·05); p=0·0007	−0·12 (−0·18 to −0·06); p=0·0002
Reliever use, number of inhalations per 24 h†	−0·64	−0·67	−0·84	−0·03 (−0·11 to 0·05); p=0·48	−0·20 (−0·28 to −0·11); p<0·0001	−0·17 (−0·25 to −0·08); p<0·0001
Nights with awakenings, %†	−13·5%	−14·0%	−16·0%	−0·6 (−2·2 to 1·1); p=0·51	−2·6 (−4·3 to −0·9); p=0·0025	−2·0 (−3·7 to −0·4); p=0·018
Asthma-control days, %†	29·3%	28·8%	31·2%	−0·5 (−3·1 to 2·2); p=0·74	1·9 (−0·7 to 4·6); p=0·16	2·4 (−0·3 to 5·1); p=0·079
ACQ-5†	−0·49	−0·53	−0·63	−0·04 (−0·10, 0·02); p=0·21	−0·15 (−0·21, −0·08); p<0·0001	−0·11 (−0·17, −0·04); p=0·0009
Lung function¶						
FEV$_1$ (L)†	−0·02	0·01	0·06	0·03 (0·001 to 0·05); p=0·043	0·08 (0·05 to 0·10); p<0·0001	0·05 (0·02 to 0·08); p=0·00014
Morning PEF (L/min)†	7·9	10·6	15·3	2·7 (−0·6 to 5·9); p=0·11	7·5 (4·2 to 10·7); p<0·0001	4·8 (1·5 to 8·0); p=0·0040
Evening PEF (L/min)†	7·5	8·5	13·8	0·9 (−2·3 to 4·1); p=0·57	6·3 (3·1 to 9·5); p=0·00014	5·4 (2·1 to 8·6); p=0·0011

All patients received budesonide-formoterol 160/4·5 µg one inhalation twice daily for maintenance therapy. ACQ-5=Asthma Control Questionnaire (5-item symptom and activity version); FEV$_1$=forced expiratory volume in 1 s; PEF=peak expiratory flow. *ANOVA. †Data are presented as adjusted mean change from run-in to the treatment period. ‡Data are presented as adjusted mean change from visit 2 (day 0) to the average value of available data during clinic visits.

Table 3: Changes from run-in in symptom control and lung function in patients using maintenance budesonide-formoterol plus alternative reliever medications

randomisation, additional increases in FEV$_1$ of 0·05 L and 0·08 L were seen with as-needed budesonide-formoterol versus formoterol (p=0·0001; figure 3) and terbutaline (p<0·0001). Mean morning PEF increased progressively from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol versus both formoterol (4·8 L per min; p=0·004) and terbutaline (7·5 L per min; p<0·0001; table 3). These improvements were maintained during the study (webfigure). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5·4 L per min; p=0·0011) and terbutaline (6·3 L per min; p=0·0001) (table 3). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline (table 3).

Use of reliever medication decreased over time in all groups, an effect that was maintained during the study (webfigure). The mean reliever use at run-in was 1·88 inhalations per day. During the treatment, this amount decreased to 1·02 inhalations per day in the budesonide-formoterol group and to 1·23 and 1·26 inhalations per day in the formoterol and terbutaline groups, respectively. Thus, the average additional dose of budesonide used by patients in the budesonide-formoterol group for maintenance and reliever therapy was 163 µg per day. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (p<0·0001 for both; table 3) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared

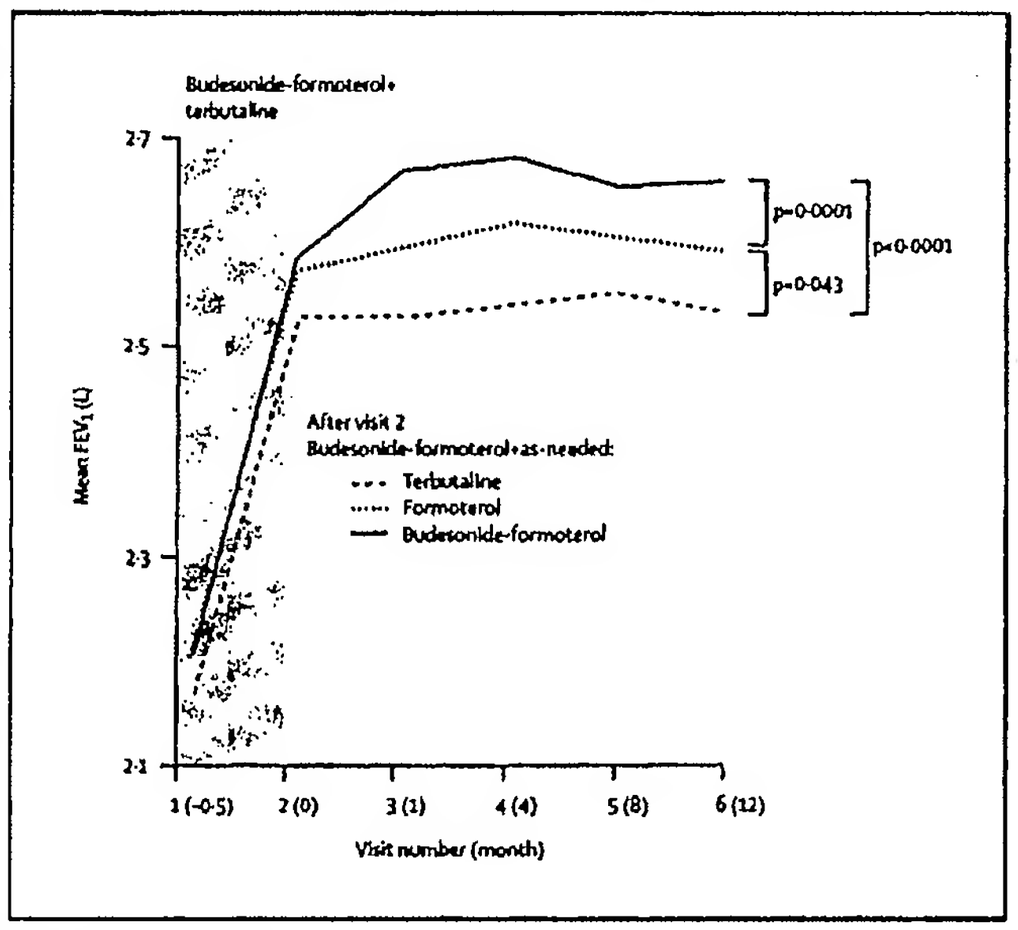

Figure 3: Mean FEV$_1$ over time
The shaded area represents the run-in period. Patients received maintenance budesonide-formoterol 160/4·5 µg, one inhalation twice daily, plus as-needed terbutaline during run-in. Post-randomisation, patients received budesonide-formoterol 160/4·5 µg 1 inhalation twice daily plus one of the following for as-needed relief: additional inhalations of budesonide-formoterol 160/4·5 µg; formoterol 4·5 µg; or terbutaline 0·4 mg. FEV$_1$=forced expiratory volume in 1 s.

	Number of patients with event (%)		
	Terbutaline as-needed group (n=1138)	Formoterol as-needed group (n=1137)	Budesonide-formoterol as-needed group (n=1107)
SAEs reported as asthma	26 (2%)	23 (2%)	16 (1%)
DAEs reported as asthma	10 (1%)	14 (1%)	1 (0·1%)
Pharmacologically predictable adverse events			
Tremor	2 (0·2%)	4 (0·4%)	1 (0·1%)
Palpitation/tachycardia	4 (0·4%)	6 (0·5%)	7 (0·6%)
Hoarseness	7 (0·6%)	11 (1%)	7 (0·6%)
Oral candidosis*	10 (1%)	11 (1%)	22 (2%)
Dysphonia	0 (0)	1 (0·1%)	0 (0)

SAE=serious adverse event. DAE=adverse event leading to discontinuation of the patient from the study. *Includes oral candidosis and any adverse event considered closely related to oral candidosis (ie, pharyngeal candidosis, oropharyngitis fungal, or oral fungal infection).

Table 4: Adverse events reported as asthma and pharmacologically predictable adverse events

with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups. In terms of weekly medication use, at run-in the median weekly as-needed reliever use (averaged over the past 10 days of run-in) was 10·5 inhalations, while during the treatment period the median as-needed use was 4·4 inhalations per week in the as-needed budesonide-formoterol group. The corresponding value for patients in the as-needed formoterol and terbutaline groups was 5·6 and 5·7 inhalations per week, respectively.

High usage of short-acting reliever is a risk factor for life-threatening asthma.[9] We thus did a post-hoc examination of patients with frequent high use of reliever therapy (arbitrarily defined as four or more as-needed inhalations on more than 100 study days [descriptive statistics only]). This pattern of high use was uncommon in all groups, being seen in 70 (6·3%) of 1107 patients in the as-needed budesonide-formoterol group, 111 (9·8%) of 1137 in the formoterol group, and 130 (11·4%) in the terbutaline group. The yearly rates per patient of severe exacerbations in outlying patients using as-needed budesonide-formoterol was 0·33, which was at least half the rate seen in outlying patients using formoterol (0·77) and terbutaline (0·76).

All treatments were well tolerated. The number of patients with non-fatal serious adverse events was comparable across groups: 70 (6·3%), 55 (4·8%), and 65 (5·7%) for the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively. Serious adverse events reported as asthma occurred in 16, 23, and 26 patients in the budesonide-formoterol, formoterol, and terbutaline groups, respectively (table 4). Discontinuations due to asthma were less common in the as-needed budesonide-formoterol group compared with the formoterol and terbutaline groups (one patient versus 14 patients and 10 patients, respectively). There were four deaths during the study (one in the as-needed budesonide-formoterol group, one in the formoterol group, and two in the terbutaline group), but none was judged by the investigator to be causally related to the study drugs and none were reported as asthma. The incidence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroids or β2 agonists was rare and comparable across all treatment groups (table 4).

Discussion

In this large, 12-month, double-blind study, we have shown that maintenance plus as-needed budesonide-formoterol reduced the risk of severe exacerbations and events resulting in emergency room visits or hospitalisations compared with maintenance budesonide-formoterol plus either formoterol or terbutaline as needed. Our study shows that the budesonide component of the budesonide-formoterol combination used when needed has a beneficial role in patients who remain symptomatic despite treatment with combination maintenance therapy.

As-needed formoterol (a rapid-acting and long-acting reliever therapy) was also seen to provide better exacerbation control compared with terbutaline. Therefore, the reduction in severe exacerbations can be attributed partly to the as-needed formoterol component of the combination. This finding extends the earlier reults of Tattersfield and colleagues,[4] who reported a similar benefit with as-needed formoterol in patients using inhaled corticosteroids alone. However, the key finding in the present study is that the budesonide component of budesonide-formoterol as needed results in additional reductions in the overall rates of severe exacerbations and emergency room visits or hospitalisations of 33% and 27%, respectively, over formoterol as needed.

The low exacerbation rate (19 events in 100 patients per year) achieved with budesonide-formoterol for maintenance and reliever therapy in the present study was obtained with 320 µg per day of maintenance budesonide plus an additional steroid dose that could vary between 0 and 1600 µg per day, depending on the patient's need for reliever medication. Although additional daily doses up

to 1600 µg were allowed in the protocol, the actual use of high doses was rare: just four patients used an average dose (maintenance plus as-needed) above 1280 µg per day of budesonide. On more than half of the treatment days, no additional inhalations were used by the budesonide-formoterol maintenance and reliever therapy group, and the average additional dose of budesonide was only 163 µg per day.

Despite the modest budesonide dose used, the exacerbation rates reported here were at least as low as those previously reported in other 12-month efficacy studies in similar patient populations using higher fixed doses of inhaled corticosteroids plus LABA[3] or titration to higher fixed doses of inhaled corticosteroids, LABA, or both.[4] The 45% reduction in the risk of a severe exacerbation with as-needed budesonide-formoterol versus terbutaline was achieved with a small (50%) increase in corticosteroid dose, comparing favourably with the 14% reduction in exacerbation risk seen with a two-fold to four-fold (100–300%) increase in maintenance corticosteroids used in several controlled trials.[6] However, the fact that self-reported drug use was not corroborated by a more accurate assessment, eg, electronic compliance monitoring, is a limitation of the study that should be considered.

The current study was mainly an efficacy study and was not specifically powered to assess rare events such as asthma mortality. Asthma-related deaths and serious adverse events have been reported to increase with LABA therapy in populations where the use of inhaled corticosteroids was not mandatory.[10,28] However, the RELIEF study,[11] which was done in 18 124 asthma patients, showed no similar associations with as-needed formoterol compared with salbutamol. In the present study, there were no asthma deaths, and the incidence of asthma-related serious adverse events was highest in the terbutaline as needed group. Discontinuations due to asthma were low in all three groups, occurring in only one in 1113 patients treated with budesonide-formoterol as needed, a rate more than 10-fold lower than that seen in either the formoterol or terbutaline as needed groups. No drug-related serious adverse events were identified with this novel regimen, and pharmacologically predictable adverse events were similar in all three treatment groups. Although adrenal function tests were not done in the present study, results of two large 1-year studies have shown that maintenance plus reliever budesonide-formoterol has a similar effect on adrenal function as budesonide 800 µg per day in adults,[9,10,21] and 400 µg per day in children.[21]

The reduction in exacerbations seen with a modest average increase in the inhaled corticosteroid dose for the budesonide-formoterol maintenance and reliever regimen suggests that a crucial factor might be related to the timing of the inhaled corticosteroid dose. After inhalation of inhaled corticosteroids, lung tissue concentrations decline over time and within 6 h values might be less than 10% of peak values.[29] Therefore, inhaled corticosteroids taken as needed might supplement the tissue concentrations of inhaled corticosteroids at a time when the concentration of inhaled corticosteroids remaining from the scheduled maintenance dose is suboptimum. The significance of tissue kinetics is suggested by the finding that, in severe unstable asthma, increasing the dose frequency from two to four-times daily while maintaining the same total daily inhaled corticosteroids dose provided greater efficacy.[30] The mechanism of action of as-needed formoterol in preventing exacerbations is also uncertain. The benefit has been suggested to be due to a stabilising effect on airway smooth muscle during an exacerbation.[31] Others have suggested that higher doses of formoterol can reduce neutrophilic inflammation.[32] Interestingly, in steroid-dependent asthma patients with acute, viral-induced exacerbations, neutrophilia rather than eosinophilia is a defining feature of the acute event.[17]

Evidence from a European study of adults with asthma has indicated that patients recognise and respond to the early signs of an impending worsening by increasing their medication. However, patients were seen to increase their short-acting β2 agonist (SABA) at the expense of their anti-inflammatory treatment.[33] The use of budesonide-formoterol for maintenance and reliever therapy could enable supplementary doses of both budesonide and formoterol to be taken early in the course of an asthma worsening, avoiding over-reliance on SABA medication. Such a treatment regimen contrasts with other approaches that rely on a substantial worsening and a formalised action plan to direct dose increases.[34,35] In such cases, late intervention has provided mixed results. In one study, a temporary increase in the dose and dose frequency of budesonide, even if initiated late in the course of a worsening, was shown to reduce the need for oral corticosteroid therapy.[35] However, a late intervention with a double dose of inhaled corticosteroids alone has been shown to be ineffective.[17,36]

Improvements in lung function, symptom scores, night-time awakenings, and reliever use were consistently greater in patients treated with budesonide-formoterol for maintenance and reliever therapy compared with formoterol or terbutaline (table 3). The improved efficacy seen in the first month of treatment with as-needed budesonide-formoterol for these secondary outcome measures was sustained throughout the 12-months of treatment. Notably, although as-needed formoterol reduced the exacerbation rate compared with as-needed terbutaline, it did not reduce as-needed medication use or symptom-related variables. Thus, although additional as-needed formoterol reduced exacerbations, daily symptoms were not affected further by increases in the formoterol dose.

Despite the availability of effective maintenance therapy, objectively assessed asthma control in the community seldom approaches guideline targets, and

preventable exacerbations are all too frequently encountered. In the RELIEF study,[9] 28–43% of 8988 patients meeting the GINA criteria for Treatment Steps III and IV had at least one exacerbation during the 6-month study. Additionally, in an observational study done in the UK, 14–21% of 588 randomly selected patients starting combination therapy for the first time needed oral steroids in the first 6 months of treatment.[10] In our study, 8–14% of patients had an exacerbation during the first 6 months of treatment. This finding suggests that our results could have applicability to a large proportion of asthma patients suitable for combination therapy. Our findings should not be extrapolated to patients with intermittent asthma, however, or to those well controlled on inhaled corticosteroids alone. Patients poorly controlled on low-dose inhaled corticosteroids have shown striking improvements in daily control and a 76% reduction in exacerbations (as defined here) when using maintenance plus as-needed budesonide-formoterol compared with a higher dose of inhaled corticosteroids alone.[4] In the present study, patients were poorly controlled on low-dose inhaled corticosteroids and LABA therapy at randomisation. Although exacerbations were reduced, and asthma control improved with budesonide-formoterol as reliever compared with either of the alternative rapid-acting β2 agonists, there remained potential for further improvement in daily control. Thus we cannot exclude the possibility that, in our study population, increases in maintenance therapy could have further improved clinical outcomes. Consequently, before this approach can be widely adopted, examination will be needed as to whether this regimen is both more effective and cost-effective compared with a higher maintenance dose of inhaled corticosteroids and LABA with short-acting β2-agonist treatment on all aspects of asthma control.

So far, budesonide-formoterol maintenance and reliever therapy has only been compared with higher maintenance inhaled corticosteroids and LABA doses in an open-label study where clinicians were free to titrate the maintenance dose of inhaled corticosteroids and LABA, as occurs in traditional practice, in both study groups. In this setting, as-needed budesonide-formoterol was able to show improvements in asthma control and allow greater reductions in maintenance therapy compared with traditional combination therapy.[11]

As-needed formoterol provides increased protection from severe exacerbations, compared with terbutaline. Furthermore, the addition of as-needed inhaled corticosteroids (budesonide) to as-needed formoterol greatly enhances this protective effect. The results from this study provide insights into our understanding of how to use inhaled corticosteroids and LABA therapy optimally to prevent asthma exacerbations. Our findings also challenge the established use of maintenance therapy plus rapid-acting β2 agonists as the only means of controlling asthma.

Contributors
All authors had unlimited access to the clinical study report and statistical analysis and contributed to the interpretation of the data. All authors were involved in every stage of manuscript preparation and the decision to submit the study article. Tito Atienza, Pál Magyar, and Umesh G Lalloo were clinical investigators in the study and contributed to the study supervision (Tito Atienza only), reviewing of the data, writing of the clinical study report, and patient recruitment. Carin Jorup and Per Larsson contributed to the study design, study planning, decisions taken during the study, writing of the statistical report/clinical trial report, interpretation of the results, and statistical analysis (Per Larsson only). All authors made final decisions on all aspects of the article and hence are in agreement with, and approve, the final version of the submitted article.

Conflict of interest statement
K Rabe has, within the last 5 years, received research funding, honoraria for lectures, and is a member of asthma advisory boards for AstraZeneca and GlaxoSmithKline. C Jorup (Senior Clinical Research Physician) and P Larsson (Statistical Science Director) are employed at AstraZeneca research and development, Lund, Sweden. U G Lalloo has been sponsored to attend an international scientific meeting by AstraZeneca. T Atienza and P Magyar declare no conflict of interest. AstraZeneca, Lund, Sweden, supported this study.

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